10. (Amended) A method of inhibiting B-cell growth in an animal comprising the step of administering a therapeutically effective amount of an antibody specific for BAFF ligand or an antigenic determinant thereof.

a3

11. (Amended) A method of inhibiting immunoglobulin production in an animal comprising the step of administering a therapeutically effective amount of an antibody specific for BAFF ligand or an antigenic determinant thereof.

12. (Amended) A method of co-inhibiting B-cell growth and immunoglobulin production in an animal comprising the step of administering a therapeutically effective amount of an antibody specific for BAFF ligand or an antigenic determinant thereof.

13. (Amended) A method of inhibiting dendritic cell-induced B-cell growth and maturation in an animal comprising the step of administering a therapeutically effective amount of an antibody specific for BAFF ligand or an antigenic determinant thereof.

IN THE DRAWINGS:

Subject to the approval of the Examiner, please replace Figure 2B with the attached replacement Figure 2B and please replace Figure 6 with the attached replacement Figure 6.

REMARKS

Claims 1-9, 14, 15, and 17-50 have been cancelled, and claims 10-13 have been amended. An Appendix of the claims marked to show the changes made is attached. No new matter has been added with these amendments, which are made solely to comply with the restriction requirement of May 20, 2002 and to clarify the language of the claims. The specification has been amended to correct a typographical error and to

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include sequence identifiers. The Sequence Listing has been revised accordingly. These amendments do not add new matter.

Formal Matters

The Examiner has objected to alleged informalities in the Drawings. Applicants have amended Figure 2B to replace "MARCH" with "BAFF." As the Examiner notes, support for this amendment can be found in the specification at page 8, lines 11-15. Applicants have amended Figure 6 to replace "KayL" with "BAFF." Support for this amendment may be found at page 9, lines 28-30. In addition, Applicants note that "KayL" and "MARCH" were merely early names for "BAFF." Thus, these amendments do not add new matter. Copies of the original drawings with proposed changes shown in red are attached, as are corrected formal drawings.

The Examiner objects to the use of the term "anti-CD11c" antibody on page 37, lines 23-24, and asserts that the "anti-CD1c" antibody was used. Applicants, however, have confirmed that anti-CD11c was, in fact, the reagent used for those studies and thus the reference to "anti-CD11c) antibody on page 37 is correct.

The Examiner has objected to the specification on page 28, line 3, for failing to provide a sequence identifier for each individual sequence. The sequence listing and the specification have been amended to conform to 37 CFR 1.821(d).

Rejections under 35 U.S.C. § 112, first paragraph

Claims 10-13 and 16 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter not enabled by the specification. The Examiner contends that the specification does not reasonably provide an enabling disclosure for practicing the claimed methods of administering a composition of any antibody specific

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for any BAFF ligand or any active fragment thereof. Applicants respectfully traverse this rejection.

Without considering the merit of the Examiner's argument, Applicants have amended the claims to more clearly set forth the intended subject matter. The claims now recite "an antibody specific for BAFF ligand or an antigenic determinant thereof," rather than an "active fragment." As a result, the Examiner's concern that the specification does not enable the production of "active fragments" of BAFF is not relevant to the pending claims.

The Examiner contends that the specification does not adequately teach how to effectively make and use any BAFF ligand, and thus, does not teach how to make and use an antibody against any BAFF ligand. Applicants disagree. The specification must be read in light of the knowledge of one of ordinary skill in the art as of the filing date of the application. The earliest effective filing date of this application is January 25, 1999. At this time, a number of BAFF ligands from different species had been isolated, cloned, and sequenced, thus enabling the production and use of these molecules. Additionally, it was known, and is taught in the instant specification, that BAFF is a member of the TNF family of molecules, and that it shares a number of structural and functional characteristics with other TNF family members (page 14, lines 5-15; page 25, line 21-page 26, line 2). Therefore, while mouse and human BAFF sequences are disclosed in the specification, it was, at the time of filing, well within the skill of one in the art to identify BAFF molecules in other species based on sequence and/or functional similarity with known BAFFs. The identification and production of a homolog to a known protein (especially a member of a very well known protein family) is routine and requires no

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undue experimentation. Therefore, the specification provides an enabling disclosure of how to make and use any BAFF molecule or antigenic determinant thereof to practice the claimed methods.

The Examiner also contends that the application fails to teach how to make and use anti-BAFF antibodies because the current state of antibody therapeutics is allegedly unpredictable due to: potential for antibody cross-reaction with irrelevant epitopes, Fc region engagement, the reduced half-life of antibody fragments, and immune response to therapeutic antibodies. The instant specification, however, deals with these potential problems and provides numerous solutions (page 16, line 11 to page 17, line 5). One skilled in the art would understand that a routine part of antibody production is testing antibodies for exactly the characteristics listed by the Examiner. Upon producing a batch of antibodies, one would run them through a series of routine tests to analyze specificity and half-life to identify possible deleterious immune responses, and then select antibodies with the appropriate properties. Therefore, one skilled in the art, using nothing more that routine laboratory tests, can predictably screen for antibodies that possess a sufficient half-life, but do not cross-react with non-specific antigens, induce Fc region engagement, or elicit a host immune response. Many such antibodies have been described in publications before this application's filing date.

Specifically, one skilled in the art can administer the Fab fragments disclosed on page 16, lines 12-16. (Gallagher et al. (2001) Intensive Care Med 27:1169-78). Fab fragments lack the Fc region, removing even the possibility of Fc region engagement. Immune responses to antibodies can also be avoided by the use of the chimeric antibodies disclosed on page 16, line 23 to page 17, line 5. A chimeric human-murine

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antibody specific for the TNF ligand (infliximab) was used successfully in Phase III clinical trials for the treatment of rheumatoid arthritis as early as 1999 (Maini et al (1999) Lancet 354(9194):1932-39). Information about these two antibody therapeutics, as well as many other applications of therapeutic antibodies, was readily available to those of ordinary skill in the art to which this application pertains as of the filing date. This information, especially as it relates to BAFF-related proteins, like TNF, renders the properties of any BAFF specific antibodies sufficiently predictable.

The Examiner contends that the specification does not provide empirical data to show the efficacy of any anti-BAFF antibody on B-cell proliferation and survival, and alleges that this efficacy could not be predicted by one skilled in the art. Additionally, the Examiner does not believe that the specification teaches the effect of BAFF ligand on B-cell isotype or that anti-BAFF antibody could inhibit all B-cell immunoglobulin production of all B-cell isotypes. In short, the Examiner does not believe that the claimed methods will work.

Applicants respectfully point out that affecting every B-cell isotype and inhibiting all immunoglobulin production is not required by the claims. The dictionary definition of "inhibit" is attached as Appendix A. The term "inhibit" when associated with biology, means to "decrease, limit, or block" activity, and is not an absolute term. Thus, the claims require only a reduction in B-cell proliferation to some level below normal, not a total prevention of all B-cell proliferation. In fact, the invention would be of little utility if all B cell growth and immunoglobulin production was completely blocked, as that would likely result in death of the animal (especially humans). Therefore, the ability or inability

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of an anti-BAFF antibody to completely block B-cell growth or immunoglobulin production is not relevant to the pending claims.

The Examiner contends that "[i]t is not clear that the skilled artisan could predict the efficacy of the anti-BAFF antibody." Applicants respectfully disagree. The instant specification teaches that BAFF binds to B cells, induces B cell proliferation, induces immunoglobulin secretion, and can induce signaling in both naive and mature B cells *in vitro*. Additionally, when overexpressed in transgenic mice, BAFF causes increased B cell populations; increased levels of immunoglobulins, rheumatoid factors, and circulating immune complexes; and lupus-like symptoms (page 34, lines 13-30; page 36, lines 1-24; page 36, line 29-page 40, line 12). Given the level of skill in the art relating to BAFF, the TNF family, and therapeutic antibodies, the instant specification provides ample disclosure of the claimed methods of treatment, enabling one skilled in the art to practice the invention without undue experimentation. For example, the specification provides information on how to synthesize antibodies, what types of antibodies to administer, and a variety of assays to assess their efficacy. Use of antibodies in TNF-related diseases is well known in the art and, when combined with Applicants' disclosure, provides ample guidelines for selection and use of appropriate antibodies, delivery methods, and dosages (Maini et al (1999) Lancet 354(9194):1932-39; Gallagher et al. (2001) Intensive Care Med 27:1169-78) in the claimed methods. Therefore, the specification provides one skilled in the art with a reasonable expectation that inhibition of BAFF will prevent B-cell proliferation and survival. It also provides a variety of assays to test the effectiveness of anti-BAFF antibodies on B-cell proliferation and survival. When these provisions are combined with the knowledge that antibody

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therapeutics have worked with respect to related proteins, and are specifically known to work for other TNF family members, one skilled in the art would not reasonably doubt the efficacy of the claimed methods.

Moreover, Applicants enclose information relating to the use of an anti-BAFF antibody in ongoing clinical trials for the treatment of autoimmune diseases (characterized by an overproduction of immunoglobulins). This information demonstrates that BAFF antibodies do affect B cell proliferation and immunoglobulin production. It is evident that the key feature of BAFF that prompted the development of the antibody therapeutic described in the Appendices was its roles in the upregulation of B-cell proliferation and inducing a lupus-like disease in animals, precisely the information disclosed in the instant specification. The synthesis and testing of the particular antibodies now in clinical trials was within the skill of one skilled in the art and cannot be considered to be anything other than routine experimentation.

Applicants respectfully submit that with the prior art and Applicants' specification in hand, one of skill in the art would be able to practice the claimed invention without undue experimentation. Accordingly, Applicants request that the rejection of claims 10-13 and 16 as lacking enablement in the specification be withdrawn.

The Examiner rejected claims 10-13 and 16 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to convey possession of the invention at the time of filing of the application. The Examiner contends that Applicants have disclosed only human and mouse BAFF sequences, and thus, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Applicants

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note for the record that the claims are drawn to methods of using antibodies that recognize BAFF.

Moreover, as noted above, the sequences of human and murine BAFF were well known in the art at the time of filing and are disclosed in the instant specification as SEQ ID NO:1 and SEQ ID NO:2. With human and murine BAFF sequences in hand, the skilled artisan is capable of identifying and cloning BAFF homologs from other species. With this BAFF homolog, one skilled in the art would be able to make a therapeutically effective antibody that recognizes and binds to BAFF based on the teachings contained in the specification (page 15, lines 13-18). The specification also provides descriptions of the methods of use of these antibodies (See page 15, line 19-page 17, line 16). Therefore, Applicants request that this rejection be withdrawn.

Double Patenting

The Examiner rejected claims 10-13 and 16 under the judicially created doctrine of obviousness-type double patenting over claims 8 of copending Application No. 10/214,065. Applicant requests that this rejection be held in abeyance until allowable subject matter is found in one of the two applications.

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

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Respectfully submitted,

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Dated: June 9, 2003

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Appendix of Replacement Paragraphs Marked to Show Changes Made

Page 1, line 4:

This application claims priority to International Application No. PCT/US00/01788 filed January 25, 2000, which claims priority to U.S.S.N. 60/117,169 filed on January 25, 1999 and U.S.S.N. 60/143,228 filed July 9, 1999 [~~2001~~]. The entire disclosures of the aforesaid patent applications are incorporated herein by reference.

Page 27, line 20:

B cell growth was efficiently costimulated with recombinant soluble BAFF lacking the transmembrane domain. This activity is in contrast to several TNF family members which are active only as membrane-bound ligand such as TRAIL, FasL and CD40L. Soluble forms of these ligands have poor biological activity which can be enhanced by their cross-linking, thereby mimicking the membrane-bound ligand (15). In contrast, cross-linking Flag-tagged sBAFF with anti-FLAG antibodies or the use of membrane-bound BAFF expressed on the surface of epithelial cells did not further enhance the mitogenic activity of BAFF, suggesting that it can act systemically as a secreted cytokine, like TNF does. This is in agreement with the observation that a polybasic sequence present in the stalk of BAFF acted as a substrate for a protease. Similar polybasic sequences are also present at corresponding locations in both APRIL and TWEAK and for both of them there is evidence of proteolytic processing (30) (N.H. and J.T, unpublished observation). Although the protease responsible for the cleavage remains to be determined, it is unlikely to be the metalloproteinase responsible for the release of membrane-bound TNF as their sequence preferences differ completely (21). The multibasic motifs in BAFF (R-N-K-R) (SEQ ID NO:23), APRIL (R-K-R-R) (SEQ ID

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NO:24) and Tweak (R-P-R-R) (SEQ ID NO:25) are reminiscent of the minimal cleavage signal for furin (R-X-K/R-R) (SEQ ID NO:26), the prototype of a proprotein convertase family (31).

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Appendix of Claims Marked to Show Changes Mad

10. A method of inhibiting B-cell growth in an animal comprising the step of administering a therapeutically effective amount of [~~a composition selected from the group consisting of:~~
~~(a) a anti-BAFF ligand molecule or an active fragment thereof;~~
~~(b) a recombinant, inoperative BAFF ligand molecule or an active fragment thereof;~~
~~(c)~~]an antibody specific for BAFF ligand or an antigenic determinant [~~active fragment~~]thereof[~~; and~~
~~(d) an antibody specific for BAFF ligand receptor or an epitope thereof~~].

11. A method of inhibiting immunoglobulin production in an animal comprising the step of administering a therapeutically effective amount of [~~a composition selected from the group consisting of:~~
~~(a) a anti-BAFF ligand molecule or an active fragment thereof;~~
~~(b) a recombinant, inoperative BAFF ligand molecule or an active fragment thereof;~~
~~(c)~~]an antibody specific for BAFF ligand or an antigenic determinant [~~active fragment~~]thereof[~~; and~~
~~(d) an antibody specific for BAFF ligand receptor or an epitope thereof~~].

12. A method of co-inhibiting B-cell growth and immunoglobulin production in an animal comprising the step of administering a therapeutically effective amount of [~~a composition selected from the group consisting of:~~
~~(a) a anti-BAFF ligand molecule or an active fragment thereof;~~
~~(b) a recombinant, inoperative BAFF ligand molecule or an active fragment thereof;~~
~~(c)~~]an antibody specific for BAFF ligand or an antigenic determinant [~~active fragment~~]thereof[~~; and~~
~~(d) an antibody specific for BAFF ligand receptor or an epitope thereof~~].

13. A method of inhibiting dendritic cell-induced B-cell growth and maturation in an animal comprising the step of administering a therapeutically effective amount of [~~a composition selected from the group consisting of:~~
~~(a) a anti-BAFF ligand molecule or an active fragment thereof;~~
~~(b) a recombinant, inoperative BAFF ligand molecule or an active fragment thereof;~~
~~(c)~~]an antibody specific for BAFF ligand or an antigenic determinant [~~active fragment~~]thereof[~~; and~~
~~(d) an antibody specific for BAFF ligand receptor or an epitope thereof~~].

16. The method according to claims 10-13, wherein the anti-BAFF receptor antibody is a monoclonal antibody.

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